

Claims:

1. A process for reducing an exocyclic double bond at the 5-position of a thiazolidinedione moiety of a thiazolidinedione precursor comprising the steps of:
  - a) preparing a solution or suspension of the thiazolidinedione precursor in a non-ether solvent medium with a base, and
  - b) combining the solution or suspension with a dithionite source.
2. A process as claimed in claim 1, wherein the solvent medium comprises an aqueous medium which comprises water or a mixture of water with one or more organic solvents.
3. A process as claimed in claim 2, wherein the organic solvent comprises an alcohol, an alkyl ester, an aromatic hydrocarbon, a halogenated hydrocarbon, an amide or a urea, or a mixture thereof.
4. A process as claimed in claim 2 or 3, wherein the organic solvent comprises methanol, ethanol, isopropanol, ethyl acetate, toluene, xylene, methylene chloride, N,N-dimethylformamide, or a mixture thereof.
5. A process as claimed in any preceding claim, wherein the dithionite source comprises sodium-, lithium-, potassium-, calcium-, magnesium-, a tetraalkylammonium- or a guanidinium-dithionite.
6. A process as claimed in any preceding claim, wherein the dithionite source is sodium dithionite.
7. A process as claimed in claim 1, wherein the base comprises an alkaline or alkaline earth carbonate, an alkaline hydrogen carbonate, an organic secondary or tertiary amine or an amidine.
8. A process as claimed in claim 7, wherein the base comprises sodium carbonate or potassium carbonate.
9. A process as claimed in any preceding claim, which process takes place in the presence of a phase-transfer catalyst.

10. A process as claimed in claim 9, wherein the phase-transfer catalyst comprises a tetrabutylammonium halide, a tetraethylammonium halide or a benzyl tributylammonium halide.
- 5 11. A process as claimed in any preceding claim, wherein the thiazolidinedione precursor is 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione or 5-[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methenyl-2,4-thiazolidinedione.
- 10 12. A process as claimed in any preceding claim, wherein the thiazolidinedione precursor is 5-[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)methoxy]phenyl]methenyl-2,4-thiazolidinedione.
- 15 13. A process as claimed in any preceding claim, wherein the solution or suspension of the thiazolidinedione precursor in the solvent medium with the base is combined with the dithionite source at elevated temperatures.
14. A process as claimed in any preceding claim, further comprising the step of isolation of the reduced thiazolidinedione precursor.
- 20 15. A process for preparing a thiazolidinedione antihyperglycemic compound comprising reduction of the exocyclic double bond at the 5-position of the thiazolidinedione moiety of the corresponding thiazolidinedione precursor which process comprises the steps of:
- 25 a) preparing a solution or suspension of the thiazolidinedione precursor in a non-ether solvent medium with a base, and heating the solution or suspension to a temperature of about 40°C to 100°C,
- b) combining the solution or suspension with a dithionite source selected from the group of sodium-, lithium-, potassium-, calcium-, magnesium-, a tetraalkyl-ammonium- or a guanidinium-dithionite, to provide a reaction mixture,
- 30 c) maintaining the reaction mixture at a temperature of about 40°C to 100°C for about 1 to 10 hours, and
- d) isolating the resulting thiazolidinedione antihyperglycemic compound as free base.
- 35 16. A process as claimed in claim 15, wherein the thiazolidinedione antihyperglycemic compound is pioglitazone, rosiglitazone or troglitazone.

17. A process for preparing pioglitazone, which process comprises the following steps:

- 5 a) preparing a solution or suspension of 5-[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl]methenyl-2,4-thiazolidinedione in a non-ether solvent medium with a base, and heating the solution or suspension to a temperature of about 60°C to 80°C,
- b) combining the solution or suspension with sodium dithionite to provide a reaction mixture,
- c) maintaining the reaction mixture at a temperature of about 60°C to 80°C for about 1 to 3 hours, and
- 10 d) isolating pioglitazone as free base.

18. A process for preparing rosiglitazone, which process comprises the following steps:

- 15 a) preparing a solution or suspension of 5-[4-[N-(2-pyridinyl)-N-methyl]ethoxy]phenyl]methenyl-2,4-thiazolidinedione in a non-ether solvent medium with a base, and heating the solution or suspension to a temperature of about 60°C to 80°C,
- b) combining the solution or suspension with sodium dithionite to provide a reaction mixture,
- c) maintaining the reaction mixture at a temperature of about 60°C to 80°C for about 1 to 3 hours, and
- 20 d) isolating rosiglitazone as free base.

19. A process as claimed in any of claims 15 to 18, wherein the reaction mixture is cooled to about 0°C to 30°C before isolation of the thiazolidinedione antihyperglycemic compound.

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20. Use of pioglitazone free base as obtained by a process as claimed in any one of claims 1 to 11 and 13 to 17, for conversion to the hydrochloride or other pharmaceutically acceptable salt form of pioglitazone.

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21. Use of a thiazolidinedione antihyperglycemic compound, as obtained according to a process as claimed in any of claims 1 to 19, for the manufacture of a medicament for the administration to a mammal in need thereof.

35 22. Use of pioglitazone as free base or as hydrochloride, as obtained by a process claimed in any of claims 1 to 11 and 13 to 17, for the manufacture of a medicament for the administration to a mammal in need thereof.

23. Use of rosiglitazone free base as obtained by a process as claimed in any one of claims 1 to 11, claims 13 to 16, or claim 18 for conversion to the maleate or other pharmaceutically acceptable salt form of rosiglitazone.

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24. Use of a dithionite source in the presence of a non-ether solvent medium to reduce selectively an exocyclic double bond at the 5-position of a thiazolidinedione moiety of a thiazolidinedione precursor to obtain the corresponding thiazolidinedione compound.

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